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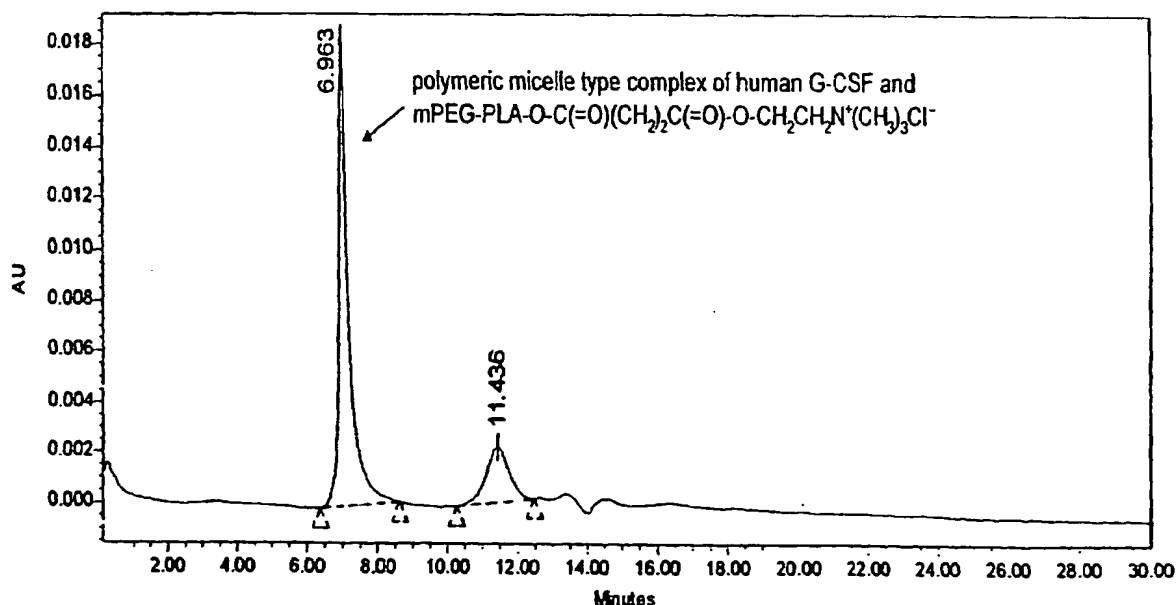
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(54) Title: POSITIVELY CHARGED AMPHIPHILIC BLOCK COPOLYMER AS DRUG CARRIER AND COMPLEX
THEREOF WITH NEGATIVELY CHARGED DRUG

Auto-Scaled Chromatogram



(57) Abstract: The present invention provides a cationic group-containing amphiphilic block copolymer that is biocompatible and biodegradable, and when used as a drug carrier for an anionic drug, provides several advantages such as increased blood concentration and improved stability of the drug.

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**POSITIVELY CHARGED AMPHIPHILIC BLOCK COPOLYMER
AS DRUG CARRIER AND COMPLEX THEREOF WITH
NEGATIVELY CHARGED DRUG**

5

TECHNICAL FIELD

The present invention relates to a positively charged drug carrier which forms a complex with a negatively charged drug. More specifically, the present invention relates to a positively charged polymeric micelle type drug carrier which comprises an A-B block type copolymer wherein A is a hydrophilic polymer block and B is a hydrophobic biodegradable polymer block and wherein one end of the hydrophobic polymer block(B) is covalently bound to one cationic group. The positively charged biodegradable block copolymer of the present invention forms a complex with a negatively charged drug via electrostatic interactions. The cationic copolymers of the present invention can be used in drug delivery and are especially useful for delivery of anionic bioactive agents.

15

BACKGROUND OF THE INVENTION

Biodegradable polymers are gaining attention as a drug delivery system. R. Langer, New Methods of Drug delivery, 249 Science 1527-1533 (1990); B. Jeong et al., Biodegradable Block Copolymers as Injectable Drug-delivery Systems, 388 Nature 860-862 (1997). Delivering bioactive agents from a biodegradable delivery system are highly desirable because the need for surgery to remove the delivery system is avoided. Controlled release of bioactive agents can reduce required frequency of administration by maintaining the concentration of a therapeutic agent at desired levels. One important means of maintaining a proper concentration is to control a degradation rate of the biodegradable drug

delivery system.

The biodegradable hydrophobic polymers widely used as drug carriers include polylactic acid(PLA), polyglycolic acid(PGA), a copolymer of lactic acid and glycolic acid(PLGA), polycaprolactone(PCL), polyorthoester(POE), polyamino acid(PAA),
5 polyanhydride(PAH), polyphosphazine, polyhydroxybutyric acid(PHB), polydioxanone(PDO), etc. Such polymers have good biocompatibility and a desirable feature of being hydrolyzed and decomposed in a living body to give side products which have no toxicity. For these reasons, they are widely used as drug carriers. In particular, since these polymers are insoluble in water formulations, some drugs are incorporated into
10 the polymer matrix and then implanted in the body in the form of microspheres, nanospheres, films, sheets, or rods, whereby the drug is slowly released and exerts a sustained therapeutic effect. In these types of formulations, the polymers themselves are finally decomposed in the body. However, these polymers have low affinity for water-soluble drugs, and so it is very difficult to incorporate a large amount of drug into the polymer matrix. Even if the drug
15 is effectively incorporated into the polymer matrix, the problem of initial burst release (which means a phenomenon whereby a large amount of drug is released within the first few hours) may occur when it is implanted into the body.

A-B, B-A-B, or A-B-A block type copolymers, wherein A is a hydrophilic polymer block and B is a hydrophobic biodegradable polymer block, have been used as drug carriers
20 for the delivery of physiologically active materials in the form of polymeric micelles, nanospheres, microspheres, gels, etc. These block copolymers have desirable properties such as good biocompatibility and ability to form core-shell type polymeric micelles in an aqueous solution where the core is composed of hydrophobic blocks and the shell is composed of hydrophilic blocks. The micellar formulation wherein a poorly water soluble

drug can be incorporated into the inside of polymeric micelle to give a micellar solution is a good drug carrier for hydrophobic drugs. However, since the drug is incorporated via hydrophobic interaction between hydrophobic drugs and hydrophobic polymer, the incorporation efficiency of highly hydrophobic drugs is excellent, but water-soluble hydrophilic drugs can hardly be incorporated into those polymeric micelles.

Kataoka et al.(EP 721,776 A1) have developed a method for incorporating a charged water-soluble drug into the inside of a polymeric micelle using a block copolymer consisting of a non-charged block and a charged block. The charged block used by Kataoka is a polyamino acid having an ionic side chain, such as polyaspartic acid, polyglutamic acid, polylysine, polyarginine, or polyhistidine. However, they are not biodegradable in a living body. In addition, since the charged block may include several functional groups having electric charges, when they are combined inside the molecule via electrostatic binding with a drug having multiple ionic groups, such as peptides or proteins, they may decrease the stability of such drugs.

In view of the foregoing, development of a drug carrier for anionic drug delivery that is biocompatible and biodegradable will be appreciated and desired. Thus, the present invention provides a new type of positively charged amphiphilic block copolymer that is biocompatible and biodegradable and that can effectively deliver the drug without decrease in its stability. By forming a complex with an anionic drug via electrostatic interaction, the cationic amphiphilic block copolymer of the present invention can effectively incorporate a water-soluble negatively charged drug into the amphiphilic block copolymer. In addition, the block copolymer of the present invention is readily susceptible to metabolic degradation after incorporation and delivery of the drug into the cell.

BRIEF SUMMARY OF THE INVENTION

The present invention provides a cationic group-containing amphiphilic block copolymer that is biocompatible and biodegradable, and provides several advantages such as increased blood concentration and improved stability of the drug when used as a drug carrier for an anionic drug. The cationic group-containing amphiphilic block copolymer of the present invention is particularly useful for delivering a drug having multiple anionic groups in the molecule, such as a peptide or protein drug, because it will prevent the drug from being decomposed enzymatically in a living body and also improve stability of the drug by inhibiting the formation of peptide-peptide or protein-protein complexes.

The present invention also provides a drug-copolymer complex wherein an anionic drug is combined via electrostatic binding with the cationic amphiphilic block copolymer above explained. Additional features and advantages of the invention will be apparent from the detailed description that follows, taken in conjunction with the accompanying drawings, which together illustrate, by way of example, features of the invention.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is an $^1\text{H-NMR}(\text{CDCl}_3)$ spectrum of $\text{mPEG-PLA-O-C(=O)(CH}_2)_2\text{C(=O)-O-CH}_2\text{CH}_2\text{N}^+\text{H}_3\cdot\text{Cl}^-$.

Figure 2 is an $^1\text{H-NMR}(\text{CDCl}_3)$ spectrum of $\text{mPEG-PLA-O-C(=O)(CH}_2)_2\text{C(=O)-O-CH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_2\text{H}\cdot\text{Cl}^-$.

Figure 3 is an $^1\text{H-NMR}(\text{CDCl}_3)$ spectrum of $\text{mPEG-PLA-O-C(=O)(CH}_2)_2\text{C(=O)-O-CH}_2\text{CH}_2\text{N}^+(\text{CH}_3)_3\cdot\text{Cl}^-$.

Figure 4 is a liquid chromatogram of human G-CSF by size exclusive chromatography.

Figure 5 is a liquid chromatogram of mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃·Cl⁻ by size exclusive chromatography.

Figure 6 is a liquid chromatogram of a complex of human G-CSF and mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃·Cl⁻ by size exclusive chromatography.

Figure 7 is a liquid chromatogram of hGH by size exclusive chromatography.

Figure 8 is a liquid chromatogram of mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃·Cl⁻ by size exclusive chromatography.

Figure 9 is a liquid chromatogram of a complex of hGH and mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃·Cl⁻ by size exclusive chromatography.

Figure 10 is an ¹H-NMR(D₂O) spectrum of diclofenac.

Figure 11 is an ¹H-NMR(D₂O) spectrum of a complex of diclofenac and mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃·Cl⁻.

Figure 12 is an ¹H-NMR(D₂O) spectrum of a mixture of diclofenac and mPEG-PLA-OH.

Figure 13 is an ¹H-NMR(D₂O) spectrum of indomethacin.

Figure 14 is an ¹H-NMR(D₂O) spectrum of a complex of indomethacin and mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₂H·Cl⁻.

DETAILED DESCRIPTION

Before getting into details of the present composition and method for delivery of a bioactive agent, it should be understood that this invention is not limited to particular

configurations, process steps, and materials disclosed herein since such configurations, process steps, and materials may vary to some extent. It should also be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limited thereby since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

In describing and claiming the present invention, the following terminology will be used in accordance with the definitions set out below.

As used herein, the term "bioactive agent" or "drug" or any other similar term means any chemical or biological material or compound suitable for administration by previously known methods in the art and/or by the methods taught in the present invention and that induce a desired biological or pharmacological effect, which may include but is not limited to (1) having a prophylactic effect on an organism and preventing an undesired biological effect such as infection, (2) alleviating a condition caused by diseases, for example, alleviating pain or inflammation caused as a result of diseases, and/or (3) alleviating, reducing, or completely eliminating diseases from the organism. The effect may be local, such as providing a local anaesthetic effect, or it may be systemic.

As used herein, the term "biodegradable" or "biodegradation" is defined as the conversion of materials into less complex intermediates or end products by solubilization hydrolysis, or by the action of biologically formed entities which can be enzymes and other products of the organism.

As used herein, the term "biocompatible" materials means materials or the intermediates or end products of materials formed by solubilization hydrolysis, or by the action of biologically formed entities which can be enzymes and other products of the organism and which cause no adverse effect to the body.

"Poly(lactide-co-glycolide)" or "PLGA" shall mean a copolymer derived from the condensation copolymerization of lactic acid and glycolic acid, or, by the ring opening polymerization of α -hydroxy acid precursors, such as lactide or glycolide. The terms "lactide," "lactate," "glycolide" and "glycolate" are used interchangeably.

5 "Poly(lactide)" or "PLA" shall mean a polymer derived from the condensation of lactic acid or by the ring opening polymerization of lactide. The terms "lactide" and "lactate" are used interchangeably.

"Biodegradable polyesters" refer to any biodegradable polyesters, which are preferably synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, 10 ϵ -caprolactone, ϵ -hydroxy hexanoic acid, γ -butyrolactone, γ -hydroxy butyric acid, δ -valerolactone, δ -hydroxy valeric acid, malic acid, and copolymers thereof.

As used herein, "effective amount" means the amount of a nucleic acid or bioactive agent that is sufficient to provide a desired local or systemic effect and performance at a 15 reasonable risk/benefit ratio as in any medical treatment.

As used herein, "peptide" means peptides of any length and includes proteins. The terms "polypeptide" and "oligopeptide" are used herein without any particular intended size limitation, unless a particular size is otherwise stated. Typical peptides that can be utilized are those selected from the group consisting of oxytocin, vasopressin, adrenocorticotrophic 20 hormone, epidermal growth factor, prolactin, luteinising hormone releasing hormone, growth hormone, growth hormone releasing factor, insulin, somatostatin, glucagon, interferon, gastrin, tetragastrin, pentagastrin, urogastroine, secretin, calcitonin, enkephalins, endorphins, angiotensins, renin, bradykinin, bacitracins, polymyxins, colistins, tyrocidin, gramicidines, synthetic analogues, modifications and pharmacologically active

fragments thereof, monoclonal antibodies, and soluble vaccines. The only limitation to the peptide or protein drug which may be utilized is one of functionality.

As used herein, a "derivative" of a carbohydrate includes, for example, an acid form of sugar, e.g. glucuronic acid; an amine of sugar, e.g. galactosamine; a phosphate of sugar,
5 e.g. mannose-6-phosphate; and the like.

As used herein, "administering" and its similar terms mean delivering the composition to an individual being treated so that the composition can be circulated systemically where the composition binds to a target cell and is taken up by endocytosis. Thus, the composition is preferably administered to the individual systemically, typically by
10 subcutaneous, intramuscular, transdermal, oral, transmucosal, intravenous, or intraperitoneal administration. Injectables for such use can be prepared in conventional forms, either a liquid solution or suspension, or a solid form that is suitable for preparation as a solution or suspension in liquid prior to injection, or as an emulsion. Suitable excipients that can be used for administration include, for example, water, saline, dextrose, glycerol,
15 ethanol, and the like; and if desired, minor amounts of auxiliary substances such as wetting or emulsifying agents, buffers, and the like. For oral administration, it can be formulated into various forms such as solutions, tablets, capsules, etc.

Reference will now be made to the exemplary embodiments and specific terms will be used herein to describe the same. It should nevertheless be understood that no limitation of
20 the scope of the present invention is thereby intended. Alterations and further modifications of the inventive features illustrated herein, and additional applications of the principles of the invention as illustrated herein, which one skilled in the relevant art could do and be aware of this disclosure, are to be considered within the scope of the invention.

The present invention relates to a block copolymer represented by the following

formula (1):



Wherein X represents a cationic group, M represents an anion, A is a biocompatible hydrophilic polymer, B is a biodegradable hydrophobic polymer, and L represents a linker
5 selected from the group consisting of -O-, -NH-, -S-, and -COO-.

The present invention also provides to a drug-polymer complex comprising a block copolymer represented by the formula (1) and a negatively charged drug wherein the anionic drug is complexed with the cationic amphiphilic block copolymer via electrostatic binding.

The positively charged polymer according to the present invention comprises an A-B
10 amphiphilic block copolymer consisting of hydrophilic blocks(A) and biodegradable hydrophobic blocks(B) wherein one terminal end of the hydrophobic blocks(B) is capped, through a linker, with one cationic group. Examples of the block copolymers include A-B-L-X wherein A is a hydrophilic block, B is a biodegradable hydrophobic block, L is a linker as defined above, and X is a cationic group.

15 The hydrophilic block(A) is a biocompatible, water-soluble and non-ionic polymer segment which includes a polyalkylene glycol such as polyethylene glycol, poly(ethylene-co-propylene)glycol, polyalkyleneoxide, polyvinylpyrrolidone, a polysaccharide, polyacrylamide, polymethacrylamide, polyvinylalcohol, and derivatives thereof, preferably polyethylene glycol, poly(ethylene-co-propylene)glycol,
20 polyvinylpyrrolidone, polyacrylamide, polyvinylalcohol, and derivatives thereof, more preferably polyethyleneglycol and derivatives thereof.

Furthermore, the biocompatible hydrophilic block (A) includes derivatives having a high molecular weight wherein said water-soluble and non-ionic polymer segments having a low molecular weight are combined together via degradable linkers. The hydrophilic block

A can be synthesized as shown in Reaction Scheme 1:

Reaction Scheme 1



wherein

- 5 Z represents a water-soluble polymer having a molecular weight of up to 5,000 Daltons, Y' represents $\text{HOOC}-(\text{CH}_2)_m-\text{COOH}$ or $\text{O}=\text{C}=\text{N}-(\text{CH}_2)_m-\text{N}=\text{C}=\text{O}$ (wherein m denotes an integer of 0 to 10), and n denotes an integer of 2 to 100.

The hydrophilic block(A) preferably has a number average molecular weight of 100 to 100,000 Daltons, and may also have any type of structure such as a single chain, a branch, etc. Examples include $\text{PEG}-\text{OOC}-(\text{CH}_2)_m-\text{COO}-\text{PEG}$ or $\text{PEG}-[\text{OOC}-(\text{CH}_2)_m-\text{COO}-\text{PEG}]_{10}-\text{OOC}-(\text{CH}_2)_m-\text{COO}-\text{PEG}$ wherein the molecular weight of PEG is up to 5,000 Daltons.

- 15 In the positively charged block copolymer according to the present invention, the biodegradable hydrophobic block(B) is preferably a biodegradable polyester synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, ϵ -caprolactone, ϵ -hydroxy hexanoic acid, γ -butyrolactone, γ -hydroxy butyric acid, δ -valerolactone, δ -hydroxy valeric acid, malic acid, and copolymers thereof. More preferably, the biodegradable polyester is synthesized from monomers selected from the group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic acid, glycolide, glycolic acid, ϵ -caprolactone, ϵ -hydroxy hexanoic acid, and copolymers thereof.

The hydrophobic B-blocks are utilized because of their biodegradable, biocompatible, and solubilization properties. The *in vitro* and *in vivo* degradations of these hydrophobic,

biodegradable polyester B-blocks are well understood and the degradation products are naturally occurring compounds that are readily metabolized and/or eliminated by a patient's body.

Examples of biodegradable hydrophobic B polymer blocks include

- 5 poly(α -hydroxyacid) or derivatives thereof such as polylactic acid(PLA), polyglycolic acid(PGA), a copolymer of lactic acid and glycolic acid(PLGA) and copolymers thereof; polyesters or derivatives thereof such as polyorthoester(POE), polyanhydride (PAH), polycaprolactone(PCL), poly(dioxan-2-one)(PDO), polyhydroxybutyric acid(PHB), a copolymer of lactic acid and dioxan-2-one(PLDO), a copolymer of caprolactone and dioxan-2-one(PCLDO), and copolymers thereof; polyphosphazine; or copolymers thereof.

Examples of preferred biodegradable hydrophobic B polymer blocks include

- poly(α -hydroxyacid) or derivatives thereof such as hydrolyzable polylactic acid (PLA), polyglycolic acid(PGA), a copolymer of lactic acid and glycolic acid(PLGA), and copolymers thereof; polyester or derivatives thereof such as polyorthoester(POE),
15 polyanhydride(PAH), polycaprolactone(PCL), poly(dioxan-2-one)(PDO), polyhydroxybutyric acid(PHB), a copolymer of lactic acid and dioxan-2-one(PLDO), a copolymer of caprolactone and dioxan-2-one(PCLDO), and copolymers thereof; or copolymers thereof. Examples of more preferred biodegradable hydrophobic B polymer blocks include polylactic acid(PLA), polyglycolic acid(PGA), polycaprolactone(PCL),
20 poly(dioxan-2-one)(PDO), a copolymer of lactic acid and glycolic acid(PLGA), or copolymers thereof.

The hydrophobic block(B) preferably has a number average molecular weight of 100 to 100,000 Daltons, and more preferably 500 to 50,000 Daltons.

The cationic group(X) in the positively charged block copolymer, according to the

present invention, is attached to the end of the hydrophobic block(B) by means of a linker L.

If the terminal end of the hydrophobic block(B) is a functional -OH, -NH₂, -SH or -COOH group, the cationic group is directly linked to the hydrophobic block(B) with the functional group providing the linker L. If not, the hydrophobic B block may be
 5 appropriately derivatized so that it may be linked to the cationic group through a suitable linker(L), such as, -O-, -NH-, -S- or -COO-. In the present invention, only one cationic group(X) can be present at the end of B hydrophobic polymer block. The cationic group is selected from those that are positively charged in aqueous solutions, preferably
 10 -C(=O)-(CH₂)_z-(C=O)-O-CH₂CH₂-Y or -C(=O)CHR¹Y wherein R¹ represents H, methyl, benzyl, 2-methylpropyl, or 1-methylpropyl, Y represents -NH₃⁺, -NRH₂⁺, -NR₂H⁺, or -NR₃⁺ wherein R represents methyl, ethyl or 2-hydroxyethyl, and z denotes an integer of 0 to 6.

M is an anion, more preferably OH⁻, Cl⁻, Br⁻, I⁻, HSO₄⁻, HCO₃⁻ or NO₃⁻.

Therefore, the positively charged block copolymer according to the present invention
 15 may have the following formula 1a:



wherein,

A is a biocompatible hydrophilic polymer block,

B is a biodegradable hydrophobic polymer block

20 L is a linker selected from the group consisting of -O-, -NH-, -S-, and COO-,

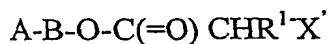
X¹ is -C(=O)-(CH₂)_z-(C=O)-O-CH₂CH₂-Y, or -C(=O)CHR¹Y

(wherein, Y is -NH₃⁺, -NRH₂⁺, -NR₂H⁺, or -NR₃⁺, R is methyl, ethyl or 2-hydroxyethyl, R¹ is H, methyl, benzyl, 2-methylpropyl or 1-methylpropyl, and z denotes an integer of 0 to

6), and

M is an anion, more preferably OH⁻, Cl⁻, Br⁻, I⁻, HSO₄⁻, HCO₃⁻ or NO₃⁻.

More specifically, the positively charged block copolymer of the present invention may have the following formula:



wherein,

A is methoxypolyethyleneglycol, polyethyleneglycol, polyvinylpyrrolidone, polyacrylamide, poly(ethylene-co-propylene)glycol, polyvinylalcohol or polysaccharide,

B is polylactide, polyglycolide, polycaprolactone, poly(dioxan-2-one), polyanhydride,
 10 poly(lactic-co-glycolide), poly(lactic-co-caprolactone), poly(lactic-co-dioxan-2-one),
 etc.,

X' is -NH₃⁺Cl⁻, -NRH₂⁺Cl⁻, -NR₂H⁺Cl⁻, or -NR₃⁺Cl⁻

(wherein, R is methyl, ethyl or 2-hydroxyethyl),

R¹ is H, methyl, benzyl, 2-methylpropyl or 1-methylpropyl, and

15 z denotes an integer of 0 to 6.

The positively charged block copolymer of the present invention is prepared by a two-step reaction which comprises synthesizing A-B block type copolymers consisting of non-ionic hydrophilic blocks(A) and hydrophobic blocks(B), and then introducing an cationic group onto the terminal end of an appropriately derivatized hydrophobic block(B).

20

1) Introduction of amino acid groups

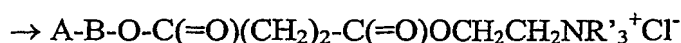
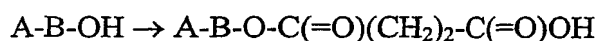


In the above scheme, L is -O-, X is C(=O)-C R¹HNH₃⁺, M is Cl⁻ and R¹ is H, methyl, benzyl, 2-methylpropyl or 1-methylpropyl.

A-B block type copolymers are reacted with an amino acid derivative bearing protection group on amino group wherein the protection group is removed after reaction, treated with an aqueous acidic solution, neutralized, dialyzed, and then lyophilized. The order of neutralization and dialysis may be reversed depending on a reagent used.

5

2) Introduction of aminoethyl groups



In the above scheme L is -O-, X is $C(=O)(CH_2)_2-C(=O)OCH_2CH_2NR'_3{}^+$, M is Cl^-

10 and R' is H, methyl, ethyl or 2-hydroxyethyl.

A-B block type copolymers are reacted with succinyl dichloride or succinyl anhydride to give A-B block type copolymers containing a terminal end of carboxylic group, condensed with aminoethanol chloride, monomethyl aminoethanol chloride, dimethyl
15 aminoethanol chloride, or choline chloride bearing protection group on amino group wherein the protection group is removed after reaction, treated with an aqueous acidic solution, neutralized, dialyzed, and then lyophilized.

The positively charged block copolymer of the present invention may form a polymeric micelle, nanoparticle or gel by incorporating the water-soluble drug, having a
20 anionic group, into the inside of the core of the core-shell type drug carrier via electrostatic binding, whereby the concentration in blood of the drug may be increased. Furthermore, peptide or protein drugs may be combined with the positively charged block copolymer of the present invention via electrostatic binding in the form of one peptide or protein molecule being surrounded by several block copolymers. In this case, decomposition of the peptide or

protein by enzymatic action in a living body may be prevented, as well as stability of the drug may be improved by the prevention of complex formation between protein-protein or peptide-peptide. The release rate of drug from the positively charged block copolymer of the present invention may be controlled by adjusting the molecular weight of the hydrophobic block(B).

The drug-copolymer complex of the present invention should be understood to include such forms as polymeric micelles, nanoparticles, gels, etc. wherein the cationic group of the positively charged block copolymer is electrostatically combined with the anionic group of the negatively charged drug to form an ionic complex, which is to be converted into the aforementioned forms in an aqueous solution. At least one positively charged block copolymer is combined with one molecule of drug in the drug-copolymer complex. This type of drug-copolymer complex may increase the concentration and half life of the drug in blood, improve stability of an unstable drug, and retard enzymatic decomposition of the drug in a living body, particularly peptide or protein drugs. If a drug contains a large number of anionic groups in the molecule, such as peptide or protein drugs, several block copolymer molecules are electrostatically combined with the drug molecule, whereby the formation of complexes between drugs is prevented, and thus stability of the drug is improved.

Drugs that can be used in the present invention include those having anionic groups in the molecule in aqueous solutions, particularly those having at least one carboxylic, phosphate or sulfate group. Preferably peptides, proteins or enzymes having at least one carboxylic group can be used. Examples include anti-cancer agents, antibiotics, anti-emetic agents, antiviral agents, anti-inflammatory and analgesic agents, anesthetic agents, anti-ulceratives, agents for treating hypertension, agents for treating hypercalcemia, agents

for treating hyperlipidemia, etc., each of which has at least one carboxylic, phosphate or sulfate group in the molecule, preferably peptides, proteins or enzymes such as insulin, calcitonin, growth hormone, granulocyte colony-stimulating factor(G-CSF), erythropoietin(EPO), bone morphogenic protein(BMP), interferon, interleukin, platelet
5 derived growth factor(PDGF), vascular endothelial growth factor(VEGF), fibroblast growth factor(FGF), nerve growth factor(NGF), urokinase, etc., each of which has at least one carboxylic, phosphate or sulfate group in the molecule.

In the process for preparing the drug-block copolymer complex of the present invention, the drug may be incorporated into the inside of the block copolymer by way of
10 simply mixing the negatively charged drug with the positively charged block copolymer in an aqueous solution; or by dissolving the negatively charged drug and the positively charged block copolymer in organic solvents such as ethanol, etc., evaporating the solvent, and dissolving the resulting mixture in an aqueous solution. As stated above, it is another characteristic of the present invention that a special method is not required for incorporating
15 the negatively charged drug into the inside of the positively charged block copolymer.

The drug-block copolymer complex according to the present invention can be administered through blood, muscle, subcutaneous tissue, bone, or local tissue, or administered orally or nasally. It can be formulated into various forms such as solutions, injectables, suspensions, tablets, capsules, etc.

20 The following examples will enable those skilled in the art to more clearly understand how to practice the present invention. It is to be understood that, while the invention has been described in conjunction with the preferred specific embodiments thereof, what follows is intended to illustrate and not to limit the scope of the invention. Other aspects of the invention will be apparent to those skilled in the art to which the invention

pertains.

EXAMPLES

The following preparations illustrate synthesis of A-B block type copolymers consisting of a hydrophilic polymer segment(A) and a hydrophobic polymer segment(B).

Preparation 1: Synthesis of monomethoxypolyethyleneglycol- polylactide (mPEG-PLA) block copolymers

5.0g of monomethoxypolyethyleneglycol(Molecular weight: 2,000 Daltons) was introduced into a two-neck 100ml round-bottomed flask, and heated to 100°C for 2-3 hours under reduced pressure(1mmHg) to remove the moisture. The inside of the reaction flask was filled with dry nitrogen and then the catalyst, stannous octoate($\text{Sn}(\text{Oct})_2$) dissolved in toluene, was added in an amount of 1.0mol%(10.13mg, 0.025mmole) with respect to the monomethoxypolyethyleneglycol. After stirring for 30 minutes, the mixture was heated to 110°C for 1 hour under reduced pressure(1mmHg) to evaporate the toluene which was used to dissolve the catalyst. 5g of purified lactide was added thereto and the resulting mixture was heated to 130°C for 12 hours. The block copolymer thus produced was dissolved in ethanol and then added to diethylether to precipitate the block copolymer. The block copolymer thus obtained was dried for 48 hours in a vacuum oven. The molecular weight of the resulting block copolymer (mPEG-PLA) was measured as 2,000-1,765 Daltons

Preparation 2: Synthesis of monomethoxypolyethyleneglycol-poly(lactic-co-glycolide)(mPEG-PLGA) block copolymers

5.0g of monomethoxypolyethyleneglycol(Molecular weight: 5,000 Daltons) was reacted with 3.72g of lactide and 1.28g of glycolide in the presence of stannous octoate at

130 °C for 6-12 hours according to the same manner as in Preparation 1, to give the title block copolymer. The molecular weight of the resulting block copolymer (mPEG-PLGA) was measured as 5,000-4,500 Daltons.

5 Preparation 3: Synthesis of monomethoxypolyethyleneglycol-
poly(lactic-co-paradioxan-2-one)(mPEG-PLDO) block copolymers

10.0g of monomethoxypolyethyleneglycol(Molecular weight: 12,000 Dalton) was reacted with 3.45 g of lactide and 1.05 g of paradioxan-2-one in the presence of stannous octoate at 110 °C for 12 hours according to the same manner as in Preparation 1, to give the
10 title block copolymer. The molecular weight of the resulting block copolymer (mPEG-PLDO) was measured as 12,000-5,400 Daltons.

Preparation 4: Synthesis of monomethoxypolyethyleneglycol- polycaprolactone
(mPEG-PCL) block copolymers

15 7.0g of monomethoxypolyethyleneglycol(Molecular weight: 12,000 Dalton) was reacted with 3.0g of ϵ -caprolactone in the presence of stannous octoate at 130 °C for 12 hours according to the same manner as in Preparation 1, to give the title block copolymer. The molecular weight of the resulting block copolymer (mPEG-PCL) was measured as
12,000-5,000 Daltons.

20 Table 1 is a summary of the results of the above preparations.

Table 1

Preparation	Block copolymer	Number Average Molecular Weight (Daltons)
1	mPEG-PLA-OH	2,000-1,765
2	mPEG-PLGA-OH	5,000-4,500
3	mPEG-PLDO-OH	12,000-5,400
4	mPEG-PCL-OH	12,000-5,000

The following examples illustrate synthesis of A-B block type copolymers containing a cationic group.

Example 1: Synthesis of methoxypolyethyleneglycol-poly lactide containing amino

5 group(-O-C(=O)CHR¹-NH₃⁺Cl⁻) (mPEG-PLA-O-C(=O)CHR¹-NH₃⁺-Cl⁻)

The block copolymer prepared in preparation 1, and having an -OH group at the terminal end of the PLA (hydrophobic B) block was reacted with an amino acid derivative bearing protecting group on amino group to give the title block copolymer.



0.583g of N-benzyloxycarbonyl glycine, 0.575g of dicyclohexyl carbodiimide(DCC) and 7.0g of methoxypolyethyleneglycol-poly lactide(mPEG-PLA, 2,000-1,765) were dissolved in 20ml of DMF. The resulting solution was reacted at room temperature for 24 hours to give N-benzyloxycarbonyl glycine methoxypolyethyleneglycol-poly lactide ester.

15 The reaction product was hydrogenized using palladium as catalyst to remove the protection group on amino group, dissolved in an aqueous hydrochloride solution, dialyzed, and then lyophilized to give 6.19g of the title block copolymer.

Examples 2 to 4: Introduction of an amino acid group

Each of the block copolymers prepared in Preparations 2 to 4 was reacted with an amino acid derivative bearing protection group on amino group according to the same manner as in Example 1 to give copolymers containing an amino acid group. The block copolymers containing an amino acid group as prepared in Examples 1 to 4 are represented in the following Table 2.

Table 2

Ex.	Block copolymer	Number Average Molecular Weight (Dalton)	
		A	B
1	mPEG-PLA-O-C(=O)CH ₂ -NH ₃ ⁺ - Cl ⁻	2,000	1,765
2	mPEG-PLGA-O-C(=O)CHCH ₃ -NH ₃ ⁺ - Cl ⁻	5,000	4,500
3	mPEG-PLDO-O-C(=O)CH(CH ₂ Ph)-NH ₃ ⁺ - Cl ⁻	12,000	5,400
4	mPEG-PCL-O-C(=O)CH(CH ₂ Ph)-NH ₃ ⁺ - Cl ⁻	12,000	5,000

Example 5: Synthesis of methoxypolyethyleneglycol-poly lactide containing

10 aminoethanol(-O-CH₂CH₂N⁺R₃ - Cl⁻) (mPEG-PLA-O-C(=O)(CH₂)_zC(=O)-O-CH₂CH₂N⁺R₃- Cl⁻)

The block copolymer prepared in Preparation 1 was reacted with dicarboxylic dichloride to give a carboxylic acid derivative and then the reaction product was reacted with 2-aminoethanol derivative to give the title block copolymer.

15 mPEG-PLA-OH + Cl-C(=O)(CH₂)_zC(=O)-Cl → mPEG-PLA-O-C(=O)(CH₂)_zC(=O)-Cl
→ mPEG-PLA-O-C(=O)(CH₂)_zC(=O)-O-CH₂CH₂N⁺R₃-Cl⁻

(wherein, z denotes an integer of 0 to 6)

7g of methoxypolyethyleneglycol-polylactide(mPEG-PLA, 2,000-1,765) and 5g of excess succinyl dichloride were dissolved in chloroform, 1ml of pyridine was added thereto, and the mixture was reacted at 60°C for 12 hours. The resulting solution was added to diethylether to precipitate the block copolymer. The precipitated block copolymer was dissolved in 10 ml of N-methyl pyrrolidone, 0.363 g of ethanolamine chloride was added thereto, and the mixture was reacted at room temperature for 12 hours. The resulting solution was diluted with distilled water, dialyzed, and then lyophilized to give 5.92g of the title block copolymer. Figure 1 is an ¹H-NMR spectrum (CDCl₃) of the block copolymer thus obtained.

Examples 6 to 11: Introduction of an amino ethanol group

Each of the block copolymers prepared in Preparations 1 to 4 was reacted with N-methylaminoethanol chloride, N,N-dimethylaminoethanol chloride or choline chloride according to the same manner as in Example 5 to give copolymers containing an aminoethanol group. The block copolymer as prepared in Examples 5 to 11 are represented in the following Table 3. Figures 2 and 3 are ¹H-NMR spectrums (CDCl₃) of the block copolymers of Examples 10 and 11, respectively.

Table 3

Ex.	Block copolymer	Number Average Molecular Weight (Dalton)	
		A	B
5	mPEG-PLA-O-C(=O)(CH ₂) ₂ C(=O)-O-CH ₂ CH ₂ N ⁺ H ₃ · Cl ⁻	2,000	1,765
6	mPEG-PLGA-O-C(=O)(CH ₂) ₃ C(=O)-O-CH ₂ CH ₂ N ⁺ (CH ₃)H ₂ · Cl ⁻	5,000	4,500
7	mPEG-PCL-O-C(=O)(CH ₂) ₆ C(=O)-O-CH ₂ CH ₂ N ⁺ (CH ₃) ₂ H · Cl ⁻	12,000	5,000

8	mPEG-PLDO-O-C(=O)(CH ₂) ₂ C(=O)-O-CH ₂ CH ₂ N ⁺ (CH ₃) ₃ · Cl ⁻	12,000	5,400
9	mPEG-PLA-O-C(=O)(CH ₂) ₂ C(=O)-O-CH ₂ CH ₂ N ⁺ (CH ₃) ₂ H · Cl ⁻	2,000	1,765
10	mPEG-PLA-O-C(=O)(CH ₂) ₂ C(=O)-O-CH ₂ CH ₂ N ⁺ (CH ₃) ₂ H · Cl ⁻	2,000	1,765
11	mPEG-PLA-O-C(=O)(CH ₂) ₂ C(=O)-O-CH ₂ CH ₂ N ⁺ (CH ₃) ₃ · Cl ⁻	2,000	1,765

Example 12: Formation of a diclofenac-containing mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻ polymeric micelle

- 5 mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻ (10 mg) as prepared in Example 11 and diclofenac(1mg) were dissolved in distilled water to give the title polymeric micelle.

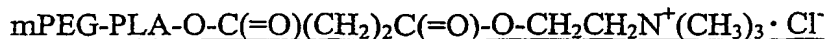
Example 13 : Formation of a Indomethacin-containing mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₂H · Cl⁻ polymeric micelle

- 10 mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₂H · Cl⁻ (10mg) as prepared in Example 10 and indomethacin (1mg) were dissolved in distilled water to give the title polymeric micelle.

Example 14: Formation of a complex of human G-CSF and mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻

- 15 mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻ (50mg) as prepared in Example 11 and G-CSF (filgrastim)(1mg) were dissolved in distilled water to give the title polymeric micelle type-complex.

Example 15: Formation of a complex of human growth hormone (hGH) and



mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻(20mg) as prepared in Example 11 and hGH(1mg) were dissolved in distilled water to give the title polymeric micelle type-complex.

5

Comparative Example 1:

mPEG-PLA-OH(10mg) as prepared in Preparation 1, which does not contain a cationic group, and diclofenac(1mg) were dissolved in distilled water. The aqueous solution obtained was lyophilized, dissolved in D₂O, and then analyzed by NMR spectroscopy. The NMR spectrum is represented in Figure 12

10

Experiment 1: Confirmation on whether a drug-block copolymer complex is formed

Human G-CSF(filgrastim) and mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻ were analyzed respectively by a size exclusive chromatography column(Pharmacia, Superdex HR 75 10/30) (concentration of human G-CSF: 50 µg/ml, injection amount: 50 microliters, mobile phase: pH 7.4 PBS, flow rate: 1ml/min). Furthermore, the polymeric micelle solution of Example 14 was analyzed according to the same manner. Figures 4, 5 and 6 are liquid chromatograms thereof. As can be seen from Figure 6, G-CSF forms a polymeric micelle type complex with mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻, and thus the peak corresponding to G-CSF disappears.

20

Experiment 2: Confirmation on whether a drug-block copolymer complex is

formed

Human growth hormone (hGH) and mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻ were analyzed respectively by a size exclusive chromatography column (Pharmacia, Superdex HR 75 10/30 or Tosoha, TSK gel G3000SW) (concentration of human hGH: 50 μg/ml, injection amount: 100 microliters, mobile phase: pH 7.4 PBS, flow rate: 1ml/min). Furthermore, the polymeric micelle solution of Example 15 was analyzed according to the same manner. Figures 7, 8 and 9 are liquid chromatograms thereof. As can be seen from Figure 9, hGH forms a polymeric micelle type complex with mPEG-PLA-O-C(=O)(CH₂)₂C(=O)-O-CH₂CH₂N⁺(CH₃)₃ · Cl⁻, and thus peak corresponding to hGH disappears.

Experiment 3: Confirmation on whether a drug-block copolymer complex is formed

Diclofenac was dissolved in D₂O and then analyzed by NMR spectroscopy. The aqueous solutions obtained in Example 12 were lyophilized, dissolved in D₂O, and then analyzed by NMR spectroscopy. The NMR spectrums are represented in Figures 10 and 11. As shown in Figure 11, in the case of the micelle solution obtained in Example 12, the peak (appearing at around 7 ppm) corresponding to H in the aromatic ring of diclofenac disappears completely and only the peak related to polyethyleneglycol is observed. This shows that there is incorporation of diclofenac into the block copolymer. To the contrary, as shown in Figure 12, both peaks corresponding to diclofenac and polyethyleneglycol are observed in the case of the micelle solution obtained in Comparative Example 1, which shows that diclofenac is not incorporated into the non-charged block copolymer.

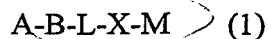
Experiment 4: Confirmation on whether a drug-block copolymer complex is formed

Indomethacin was dissolved in D₂O and then analyzed by NMR spectroscopy. The aqueous solution obtained in Example 13 was lyophilized, dissolved in D₂O, and then analyzed by NMR spectroscopy. The NMR spectrums are represented in Figures 13 and 14. As shown in Figure 14, in the case of the micelle solution obtained in Example 13, the peak (appearing at around 7 ppm) corresponding to H in the aromatic ring of indomethacin sodium salt disappears completely and only the peak related to polyethyleneglycol is observed. This shows that there is incorporation of indomethacin into the block copolymer.

It is to be understood that the above-described embodiments are only illustrative of the applications of the principles of the present invention. Numerous modifications and alternative embodiments can be derived without departing from the spirit and scope of the present invention and the appended claims are intended to cover such modifications and arrangements. Thus, while the present invention has been shown in the drawings and fully described above with particularity and detail in connection with what is presently deemed to be the most practical and preferred embodiment(s) of the invention, it will be apparent to those of ordinary skill in the art that numerous modifications can be made without departing from the principles and concepts of the invention as set forth in the claims.

CLAIMS

1. A block copolymer having the formula:



wherein X represents a cationic group, M represents an anion, A is a biocompatible

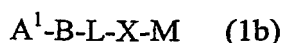
- 5 hydrophilic polymer, B is a biodegradable hydrophobic polymer, and L represents a linker selected from the group consisting of -O-, -NH-, -S- and -COO-.

2. The block copolymer of claim 1 wherein the number average molecular weight of A and B each is within the range of 100 to 100,000 Daltons.

3. The block copolymer of claim 1 wherein X is $-\text{C}(=\text{O})-(\text{CH}_2)_z-\text{C}(=\text{O})-\text{O}-\text{CH}_2\text{CH}_2-\text{Y}$ or $-\text{C}(=\text{O})\text{CHR}^1\text{Y}$ wherein R^1 is H, methyl, benzyl, 2-methylpropyl or 1-methylpropyl, Y is $-\text{NH}_3^+$, $-\text{NRH}_2^+$, $-\text{NR}_2\text{H}^+$, or $-\text{NR}_3^+$ wherein R is methyl, ethyl or 2-hydroxyethyl, and z denotes an integer of 0 to 6.

4. The block copolymer of claim 1 wherein M is OH^- , Cl^- , Br^- , I^- , HSO_4^- , HCO_3^- or NO_3^- .

- 15 5. A block copolymer having the formula:



wherein X represents a cationic group, M represents an anion, A^1 is a biocompatible

hydrophilic polymer, B is a biodegradable hydrophobic polymer, L represents a linker

selected from the group consisting of -O-, -NH-, -S- and -COO-, wherein A^1 is one selected

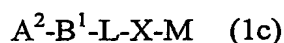
- 20 from the group consisting of polyalkyleneglycol, polyalkyleneoxide, polyvinylpyrrolidone, polysaccharide, polyacrylamide, polymethacrylamide, polyvinylalcohol, and derivatives thereof and B is a biodegradable polyester.

6. The block copolymer of claim 5 wherein the number average molecular weight of A^1 and B is within the range of 100 to 100,000 Daltons.

7. The block copolymer of claim 5 wherein X is $-C(=O)-(CH_2)_z-C(=O)-O-CH_2CH_2-Y$ or $-C(=O)CHR^1Y$ wherein R^1 is H, methyl, benzyl, 2-methylpropyl or 1-methylpropyl, Y is $-NH_3^+$, $-NRH_2^+$, $-NR_2H^+$, or $-NR_3^+$ wherein R is methyl, ethyl or 2-hydroxyethyl, and z denotes an integer of 0 to 6.

5 8. The block copolymer of claim 5 wherein M is OH^- , Cl^- , Br^- , I^- , HSO_4^- , HCO_3^- or NO_3^- .

9. A block copolymer having the formula:



wherein X represents a cationic group, M represents OH^- or an anion, A^2 is a biocompatible
 10 hydrophilic polymer, B^1 is a biodegradable hydrophobic polymer, L represents a linker
 selected from the group consisting of $-O-$, $-NH-$, $-S-$ and $-COO-$, wherein A^2 is one selected
 from the group consisting of polyalkyleneglycol, polyalkyleneoxide, polyvinylpyrrolidone,
 polysaccharide, polyacrylamide, polymethacrylamide, polyvinylalcohol, and derivatives
 thereof and B^1 is a biodegradable polyester synthesized from monomers selected from the
 15 group consisting of D,L-lactide, D-lactide, L-lactide, D,L-lactic acid, D-lactic acid, L-lactic
 acid, glycolide, glycolic acid, ϵ -caprolactone, ϵ -hydroxy hexanoic acid, and copolymers
 thereof.

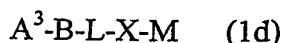
10. The block copolymer of claim 9 wherein the number average molecular weight of A^2 and B^1 each is within the range of 100 to 100,000 Daltons.

20 11. The block copolymer of claim 9 wherein X is $-C(=O)-(CH_2)_z-C(=O)-O-CH_2CH_2-Y$ or $-C(=O)CHR^1Y$ wherein R^1 is H, methyl, benzyl, 2-methylpropyl or 1-methylpropyl, Y is $-NH_3^+$, $-NRH_2^+$, $-NR_2H^+$, or $-NR_3^+$ wherein R is methyl, ethyl or 2-hydroxyethyl, and z denotes an integer of 0 to 6.

12. The block copolymer of claim 9 wherein M is OH^- , Cl^- , Br^- , I^- , HSO_4^- , HCO_3^- or

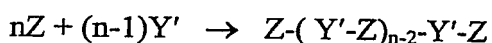
NO₃⁻.

13. A block copolymer having the formula:



wherein X represents a cationic group, M represents an anion, A³ is a biocompatible

5 hydrophilic polymer, B is a biodegradable hydrophobic polymer, L represents a linker selected from the group consisting of -O-, -NH-, -S- and -COO-, and wherein A³ is a degradable derivative prepared according to the following reaction scheme:



wherein Z represents a water-soluble polymer having a molecular weight of up to 5,000

10 Daltons, Y' represents HOOC-(CH₂)_m-COOH or O=C=N-(CH₂)_m-N=C=O wherein m is an integer of 0 to 10, and n is an integer of 2 to 100.

14. The block copolymer of claim 13 wherein the number average molecular weight of A³ and B each is within the range of 100 to 100,000 Daltons.

15. The block copolymer of claim 13 wherein X is
15 -C(=O)-(CH₂)_z-(C=O)-O-CH₂CH₂-Y or -C(=O)CHR¹Y wherein R¹ is H, methyl, benzyl, 2-methylpropyl or 1-methylpropyl, Y is -NH₃⁺, -NRH₂⁺, -NR₂H⁺, or -NR₃⁺ wherein R is methyl, ethyl or 2-hydroxyethyl, and z denotes an integer of 0 to 6.

16. The block copolymer of claim 13 wherein M is OH⁻, Cl⁻, Br⁻, I⁻, HSO₄⁻, HCO₃⁻ or NO₃⁻.

20 17. A composition comprising the block copolymer of claim 1 and a negatively charged drug wherein the block copolymer combines with the negatively charged drug via electrostatic forces and forms a drug-block copolymer complex.

18. A composition comprising the block copolymer of claim 5 and a negatively charged drug wherein the block copolymer combines with the negatively charged drug via

electrostatic forces and forms a drug-block copolymer complex via electrostatic forces and forms a drug-block copolymer complex.

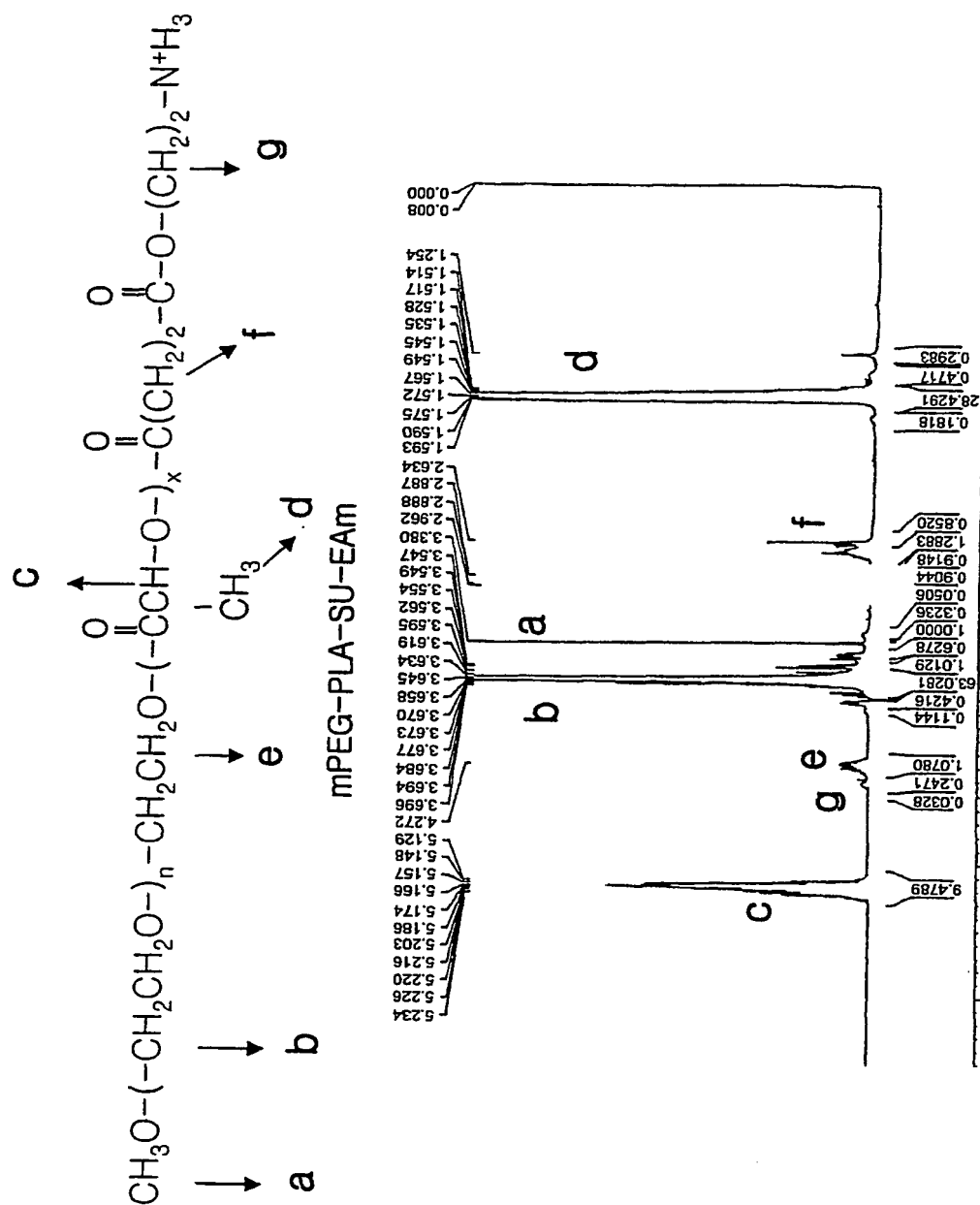
19. A composition comprising the block copolymer of claim 9 and a negatively charged drug wherein the block copolymer combines with the negatively charged drug via electrostatic forces and forms a drug-block copolymer complex via electrostatic forces and forms a drug-block copolymer complex.

20. A composition comprising the block copolymer of claim 13 and a negatively charged drug wherein the block copolymer combines with the negatively charged drug via electrostatic forces and forms a drug-block copolymer complex via electrostatic forces and

forms a drug-block copolymer complex.

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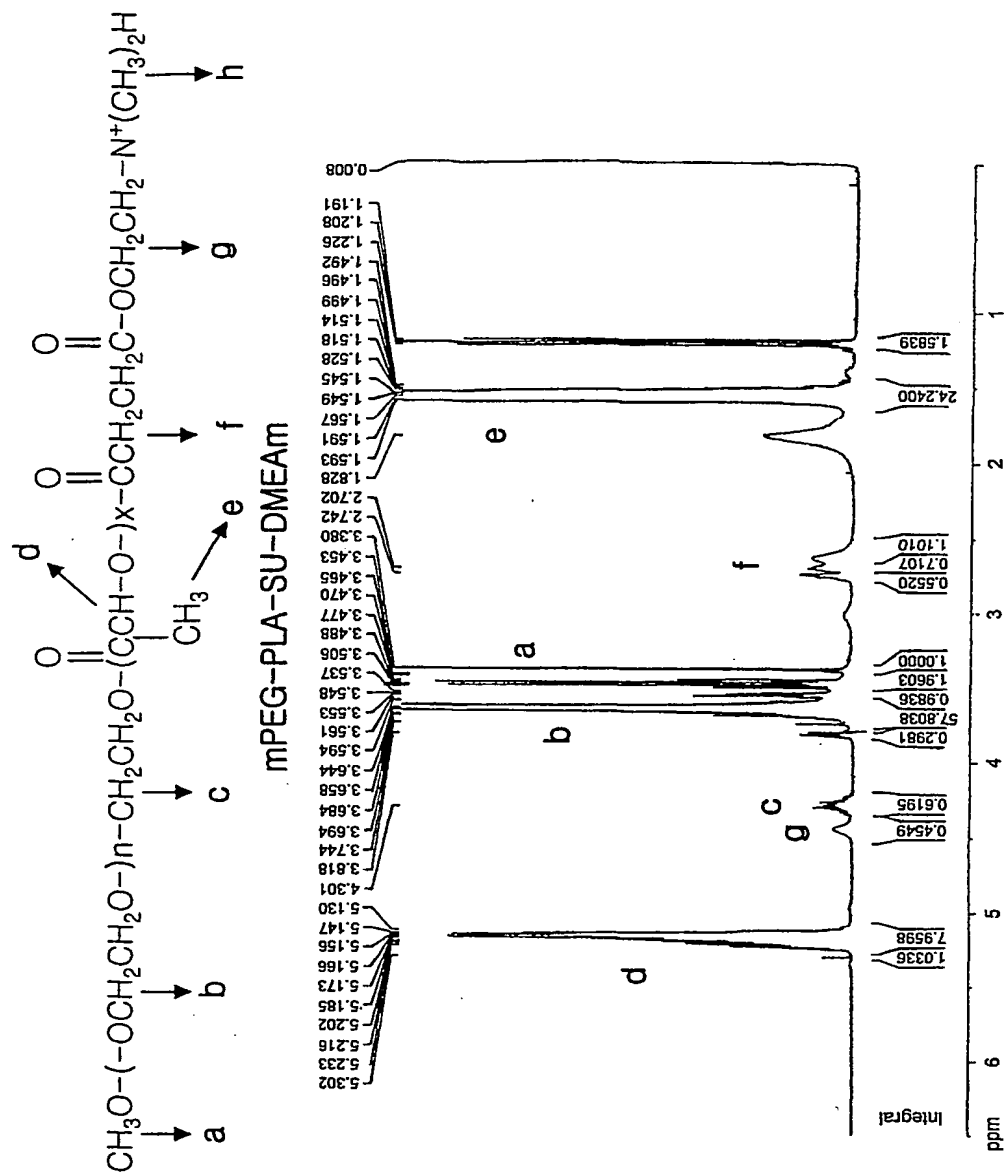
FIG. 1



¹H-NMR spectrum(CDCl₃) of mPEG-PLA-OCO-(CH₂)₂-CO-O-(CH₂)₂-N⁺H₃ Cl⁻

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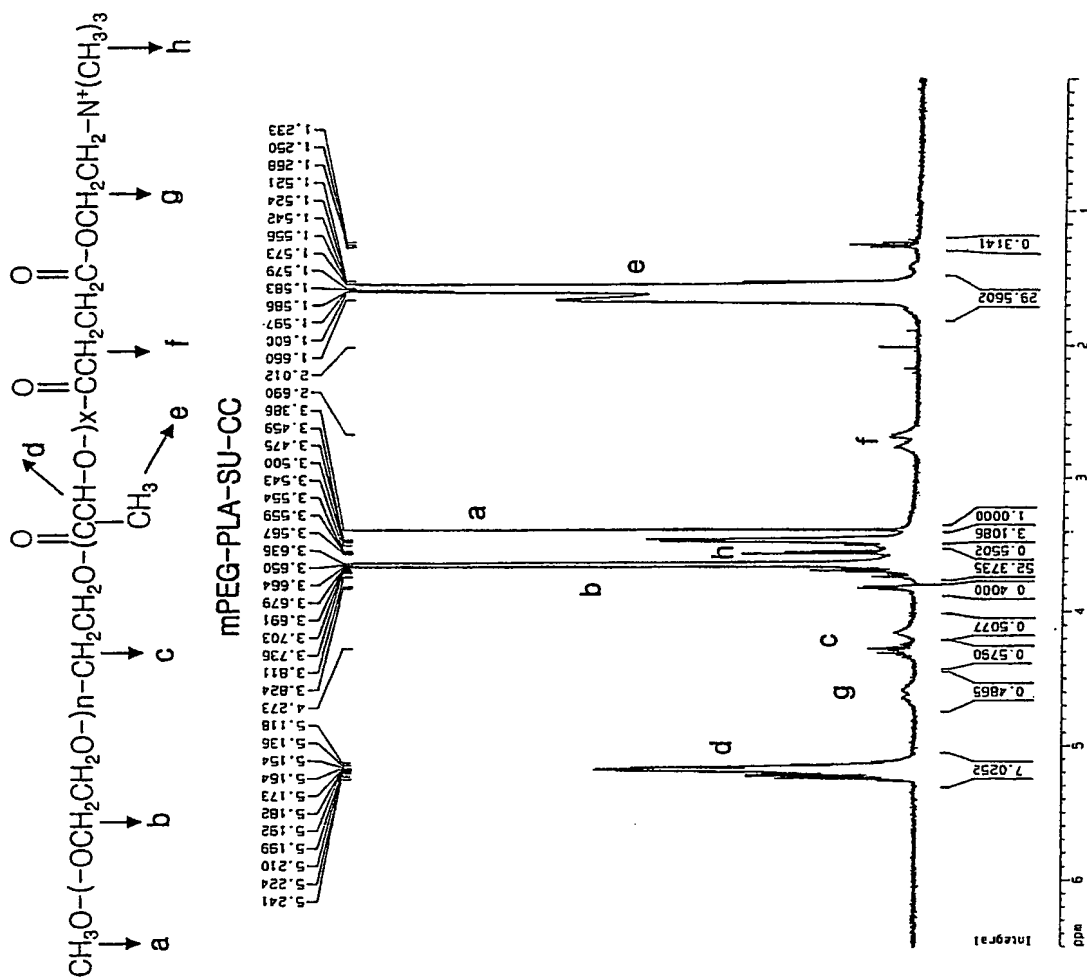
FIG. 2



¹H-NMR spectrum(CDCl₃) of m-PEG-PLA-OCO-(CH₂)₂-CO-O-(CH₂)₂-N⁺(CH₃)₂HCl⁻

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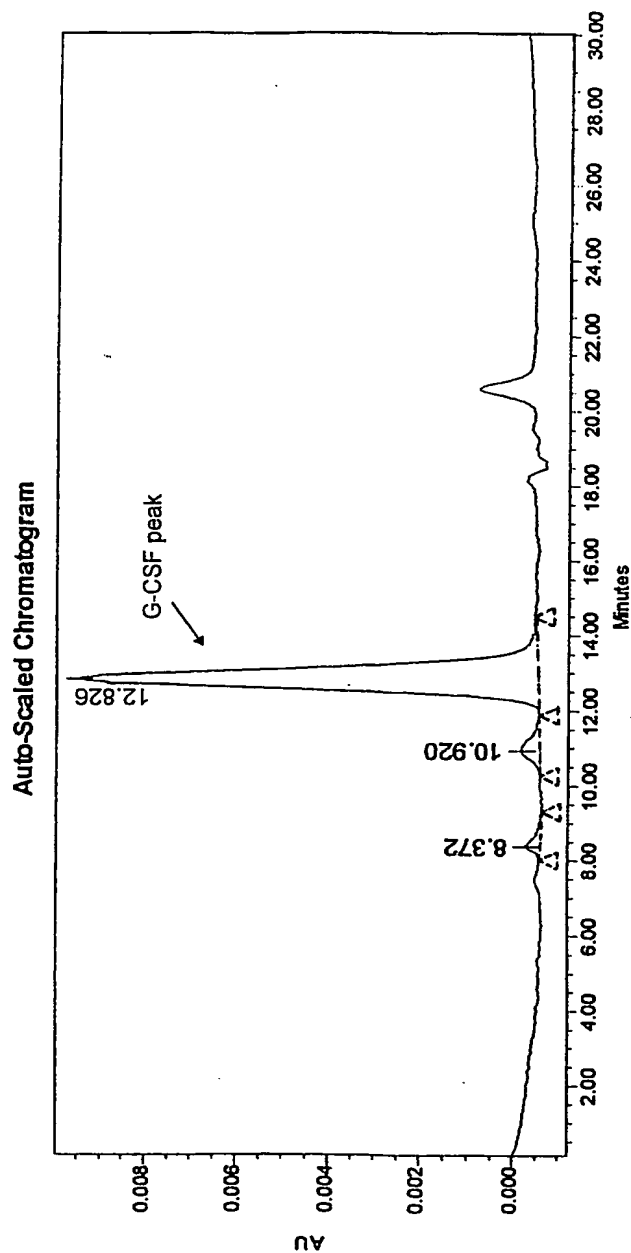
FIG. 3



^1H -NMR spectrum (CDCl₃) of m-PEG-PLA-OCO-(CH₂)₂-CO-O-(CH₂)₂-N⁺(CH₃)₃ Cl⁻

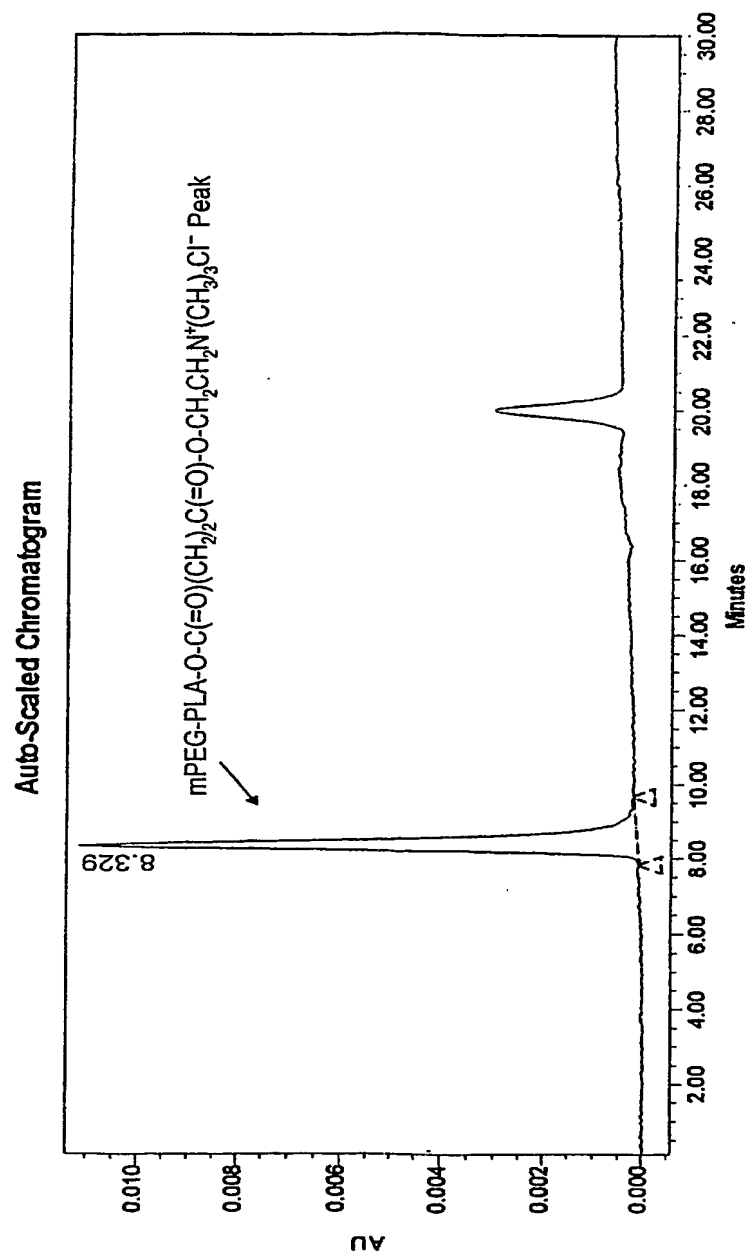
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FIG. 4



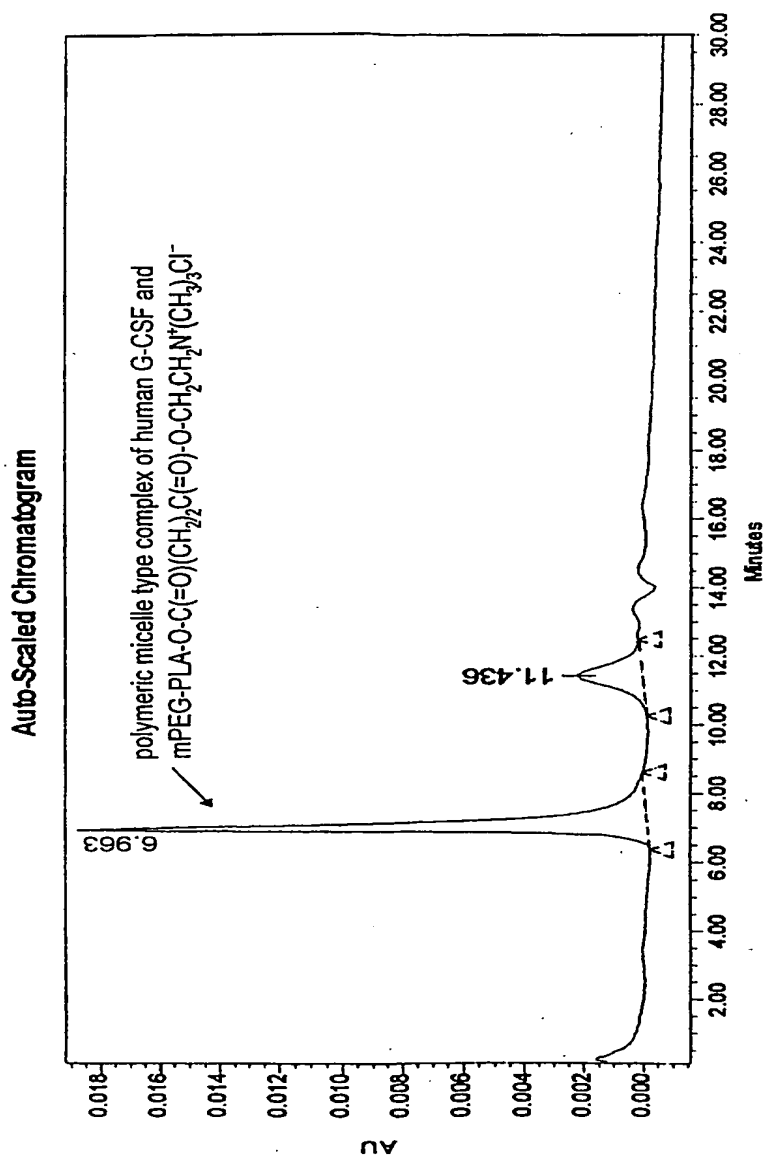
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FIG. 5



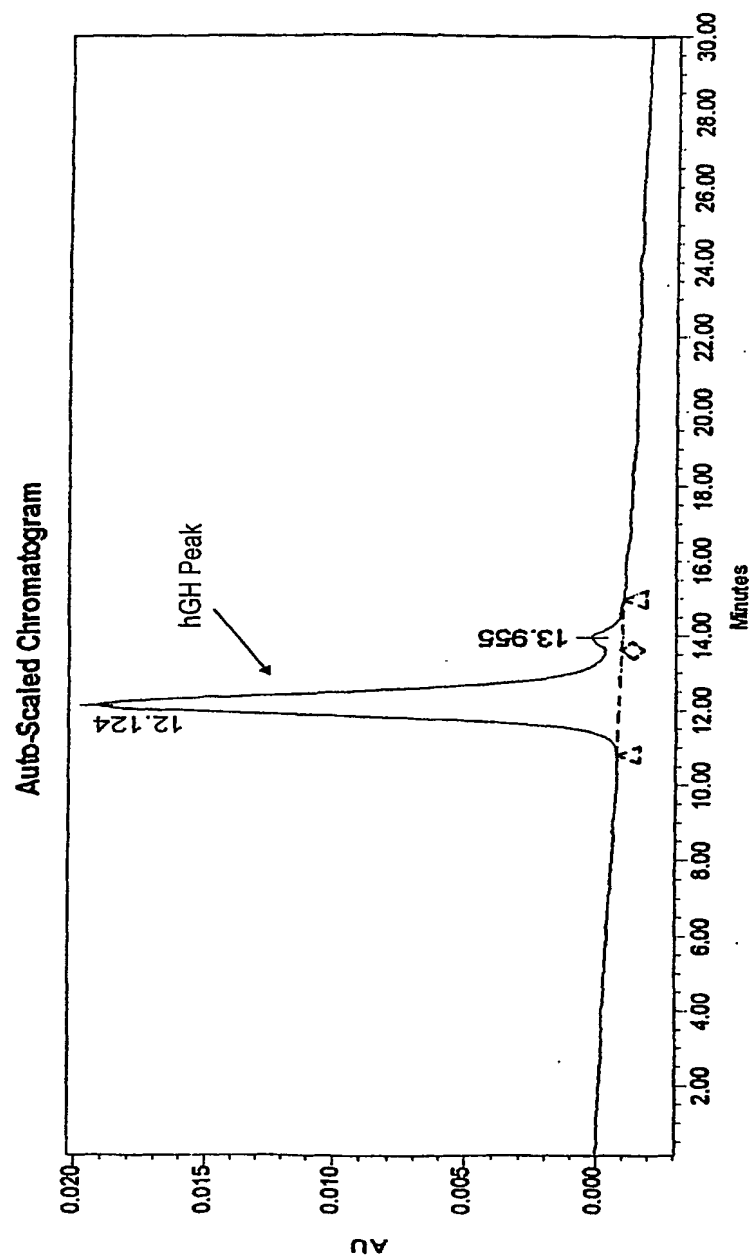
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FIG. 6



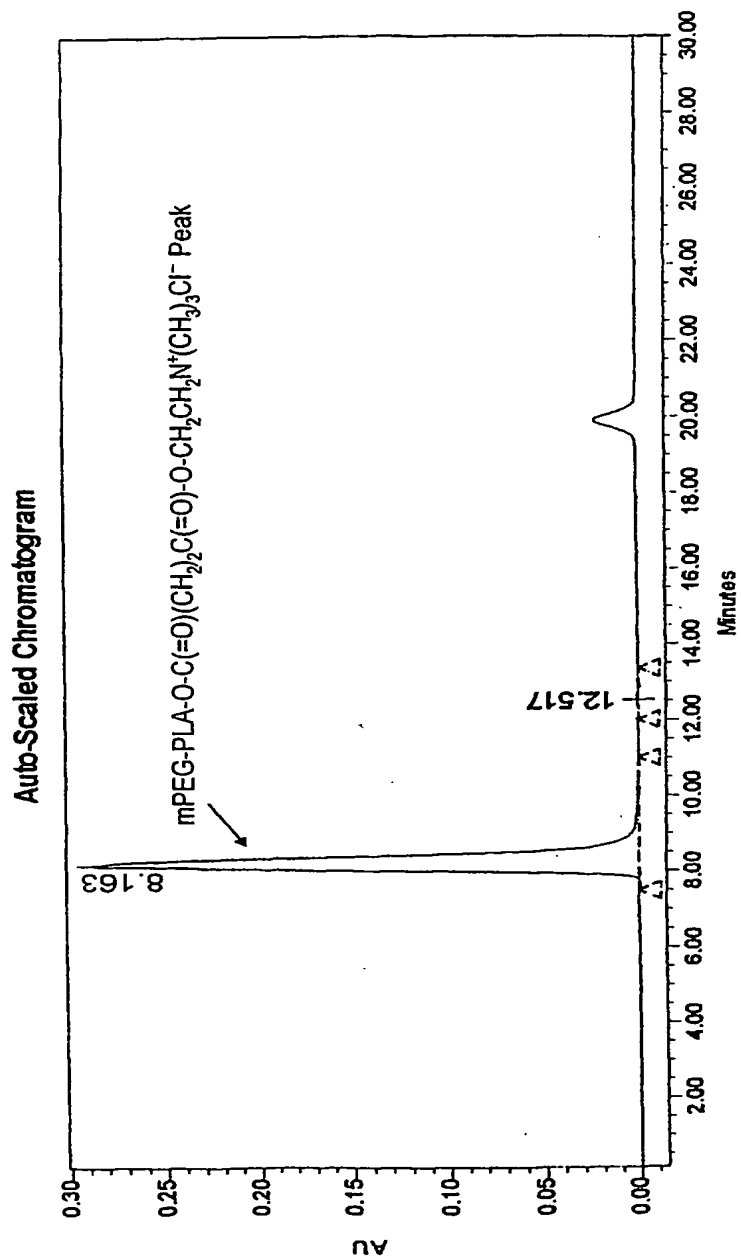
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FIG. 7



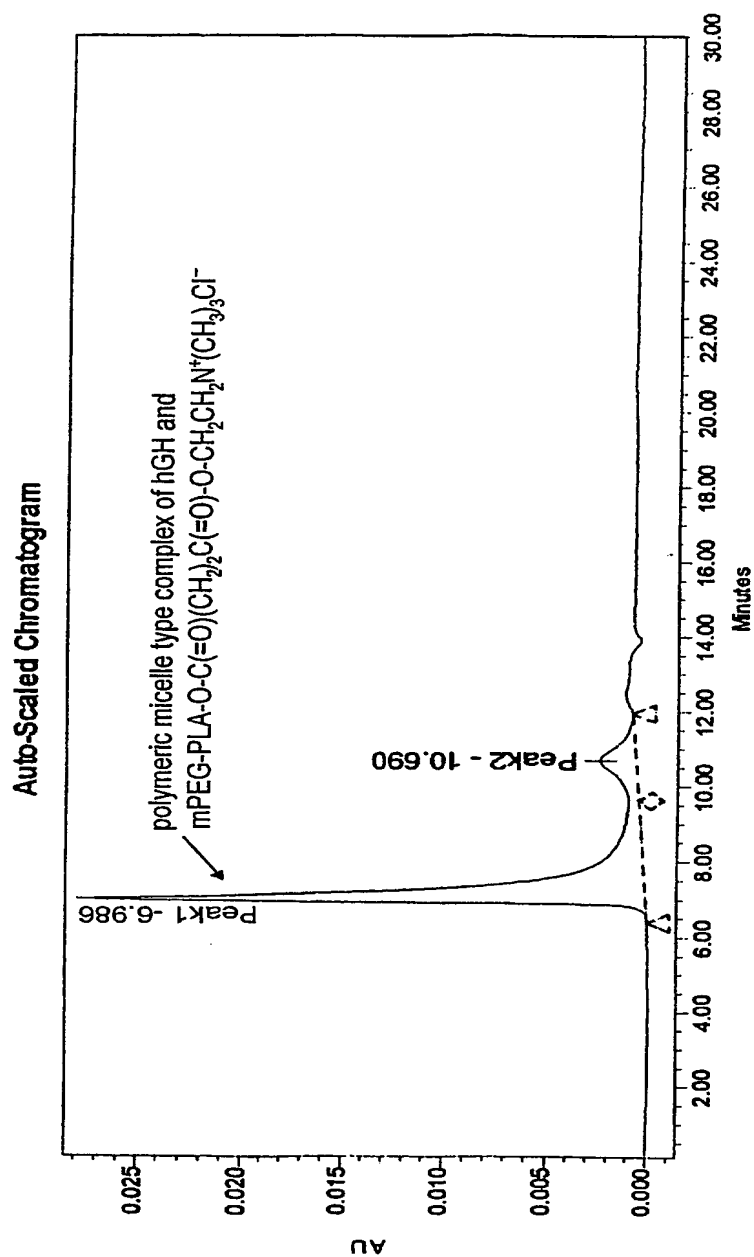
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FIG. 8



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FIG. 9



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FIG. 10

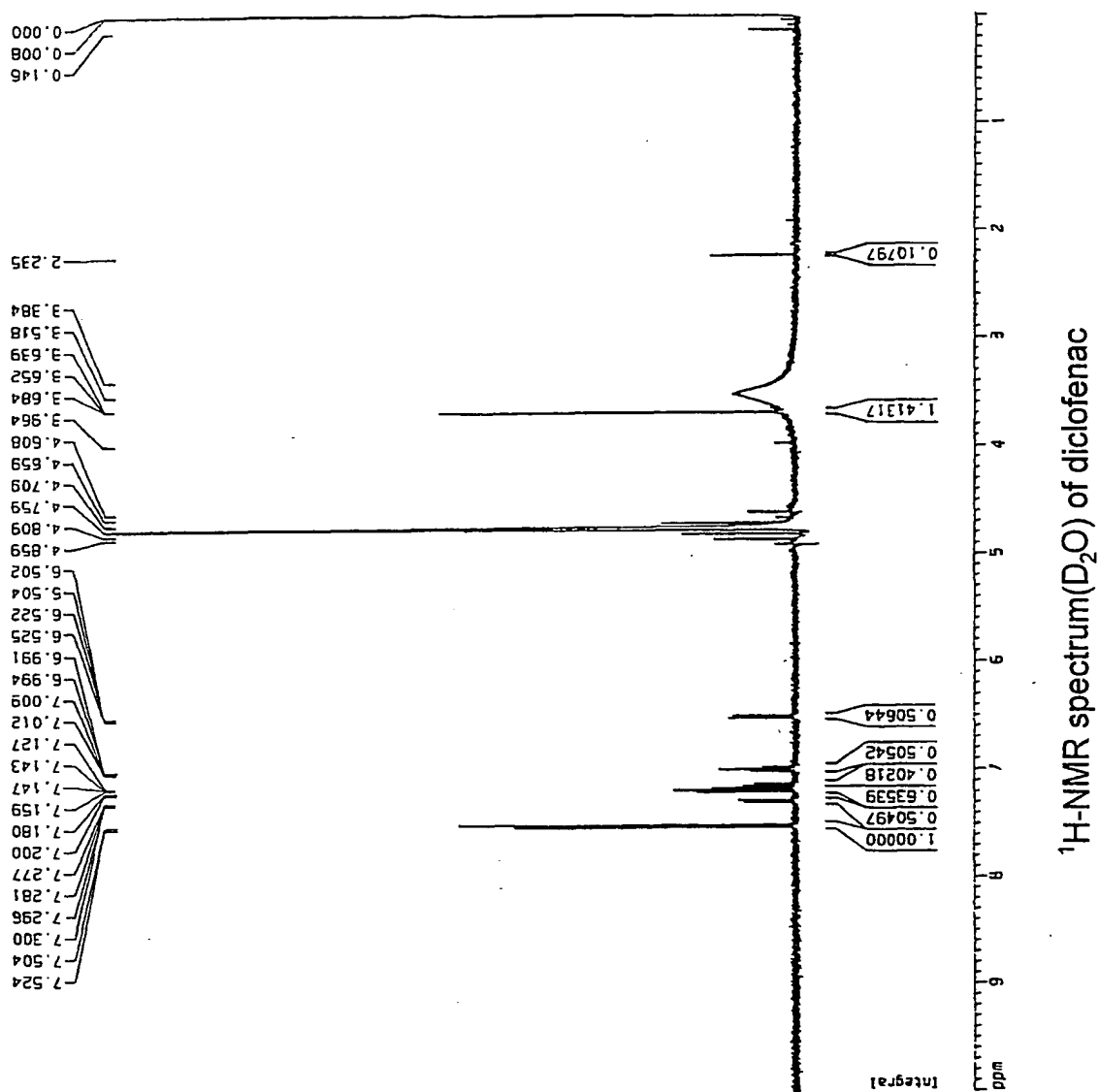
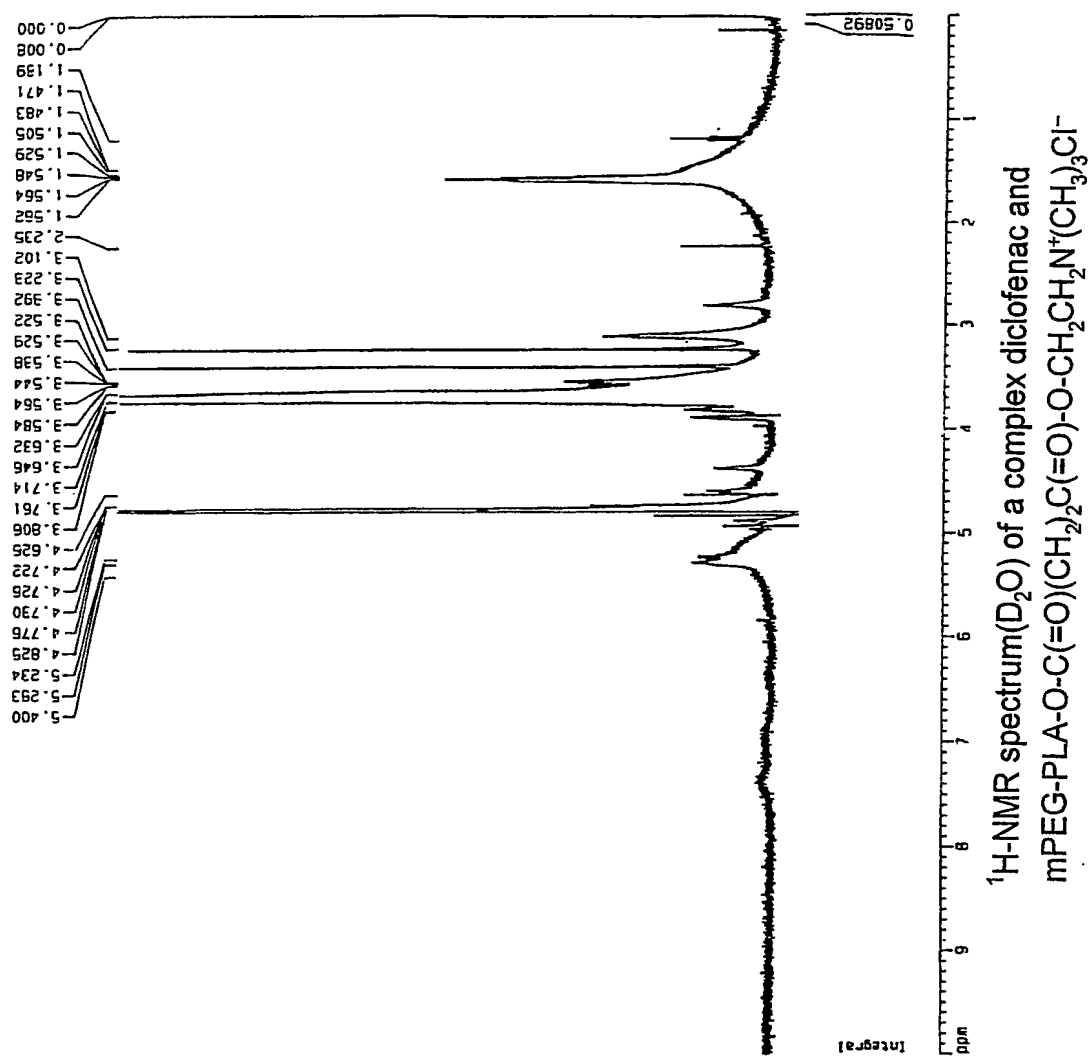
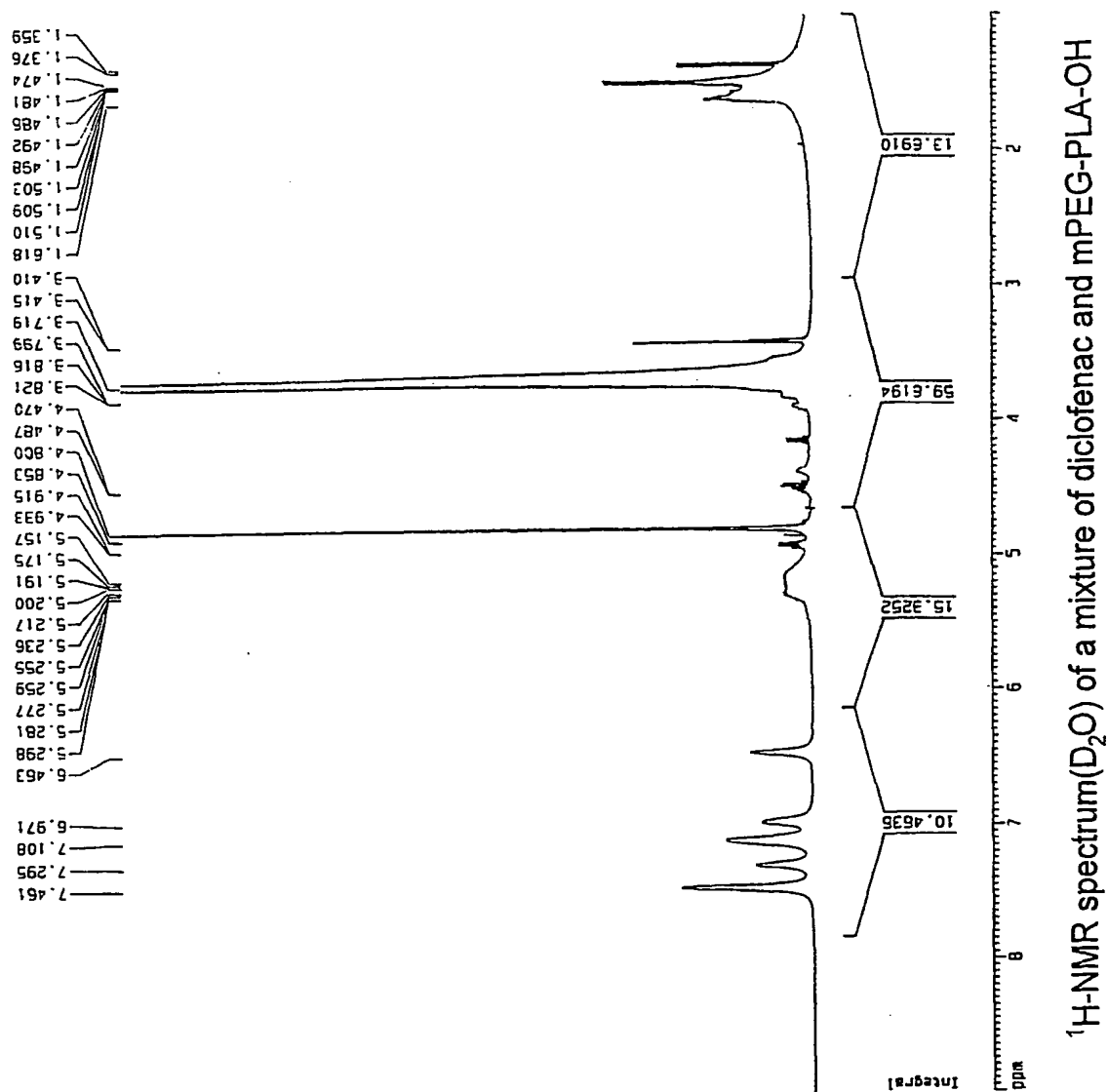


FIG. 11



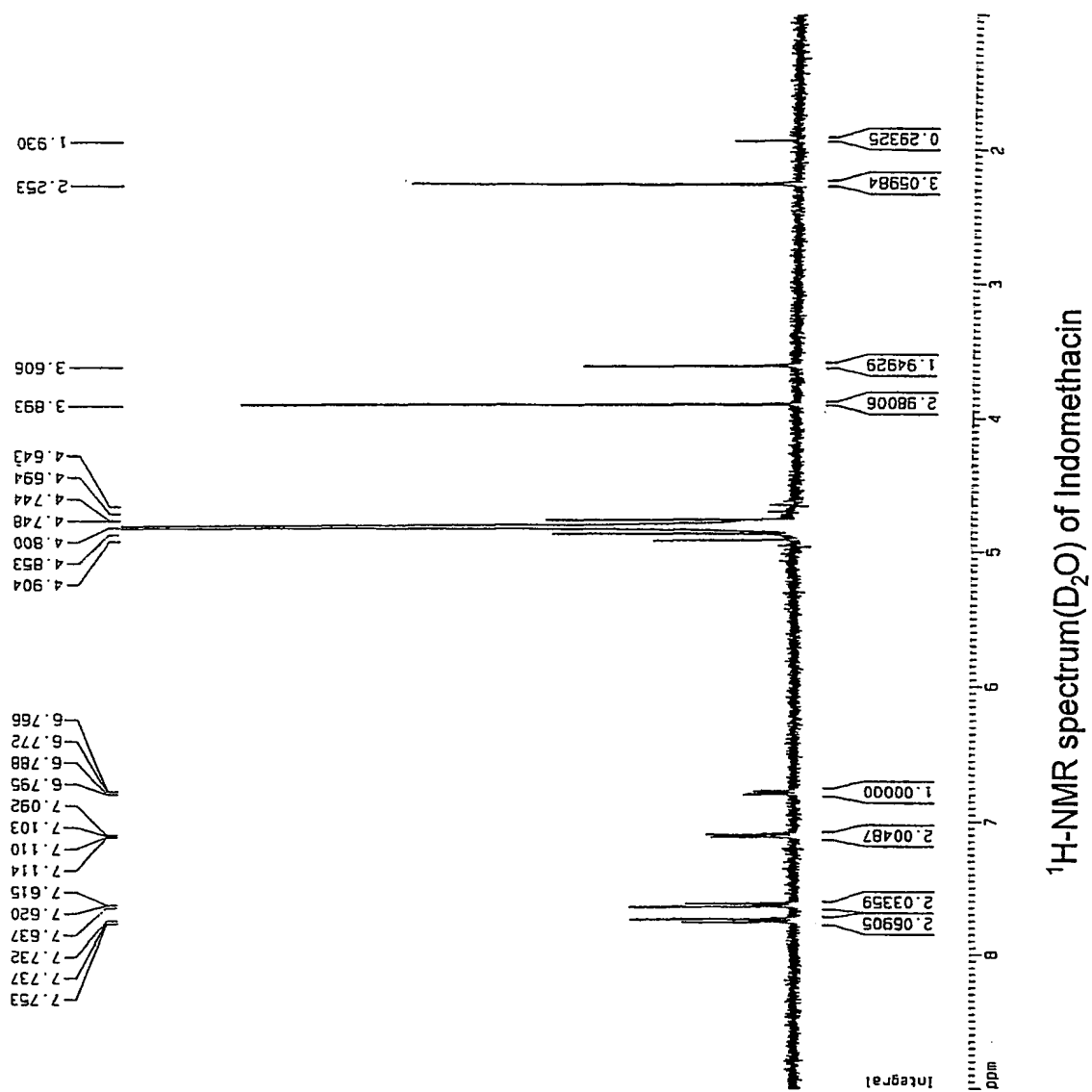
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FIG. 12



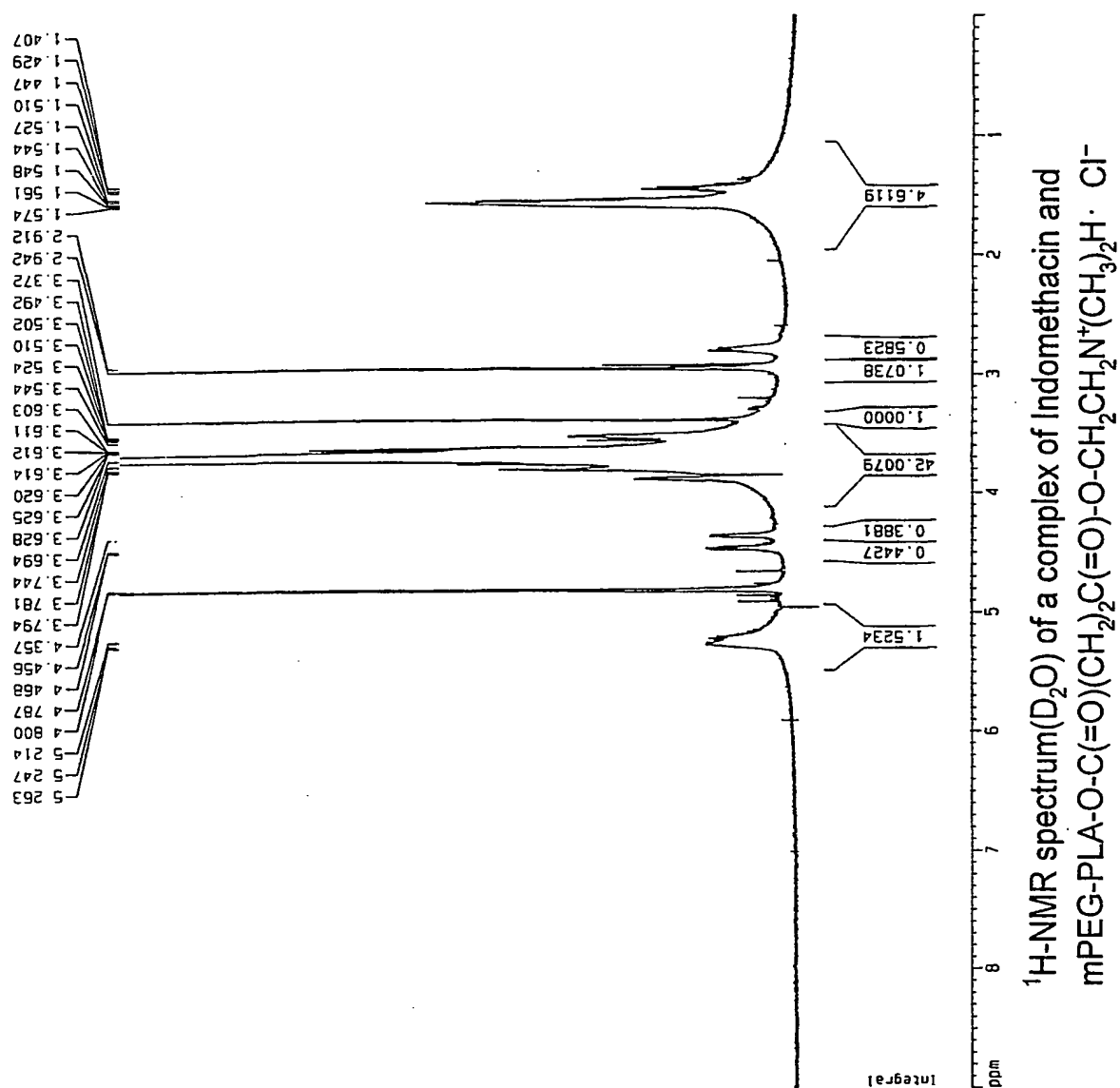
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FIG. 13



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FIG. 14



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 02/01328

CLASSIFICATION OF SUBJECT MATTER

IPC⁷: C08G 63/91, A61K 47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC⁷: A61K, C08G

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DEPATISNET, EPODOC, PAJ, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99/18142 A1 (MACROMED, INC.) 15 April 1999 (15.04.99) <i>claims.</i>	1,2,5,6,9,10,13 , 14,17
A	WO 97/10849 A1 (SAM YANG CO. LTD.) 27 March 1997 (27.03.97) <i>claims.</i>	1,2,5,6,9,10,13 , 14,17
A	WO 00/18821 A1 (MACROMED, INC.) 6 April 2000 (06.04.00) <i>claims.</i>	1,2,5,6,9,10,13 , 14,17

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR 02/01328-0

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